PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

13 SEP 2004

Applicant's or agent's file reference P3060 WO ORD	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/GB 03/01015	International filing date *(day/month/year)* 10.03.2003	Priority date *(day/month/year)* 13.03.2002
International Patent Classification (IPC) or both national classification and IPC C08J3/20, C08J3/20		
Applicant UNIVERSITY OF NOTTINGHAM		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 6 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
14.08.2003	16.06.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Otegui Rebollo, J Telephone No. +49 89 2399-8670

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB 03/01015

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-44 as originally filed

Claims, Numbers

1-24 received on 03.06.2004 with letter of 03.06.2004

Drawings, Sheets

1/6-6/6 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☒ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

   see separate sheet

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 23,24

   because:

   ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 23,24

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1-22
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-22
Industrial applicability (IA)	Yes:	Claims	1-22
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item I

Basis of the report

The formulation of claim 1 of the present application offends Article 34(2) PCT in that it is not apparent which material is actually sprayed (see claim 5 as originally filed). The same applies to claim 6 as far as the nature of the polymer substrate, as described in example 2 of the application, is not recited therein. Likewise claim 22 appears to have been extended its scope over the subject-matter of originally filed claim 25, on which it apparently rests.

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The subject-matter of claims 23 and 24 of the application has not been searched (Article 17(2)(a)(ii) and (2)(b) PCT). Therefore, claims 23 and 24 need not be the subject of an international preliminary examination (Rule 66(1)(e) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: WO-A-9815348
D2: WO-A-0168054
D3: XP-2142912
D4: WO-A-9851347
D5: WO-A-9418264

1. The subject-matter of claims 1 to 22 of the present application is novelty anticipated (Article 33(2) PCT) by the methods of preparing controlled release materials and the resulting composite materials prepared in documents D2 (see in particular the preferred process variants 1 to 3 on page 9) and D3 (see passages cited in the search report). Note also that the particles deposited in D2 are very small, and implicitly very well distributed, see for instance page 10, first paragraph. Applicants' attention is also drawn

to the fact that a composition or composite material is not automatically novel when is prepared by a different process, this process must be shown to always and unequivocally provide the resulting composition or composite material with least a differing material feature from the known compositions or composites. Therefore, the composites prepared in D4 and D5 (see passages cited in the search report) also appear to anticipate the subject-matter of claim 21. Concerning the issue of polymer substrate swellability, applicants' attention is drawn to the following passage of WO-A-98/34596, page 57, lines 11 to 16: "The water solubility of the PHAs is dependent on the molecular weight and the nature of the end groups. For example, non-esterified polylactic acid is water-soluble up to a molecular weight of 522 (7 repeat units) with some authors reporting up to 882 (12 repeat units) as being water-soluble. Acetylated polylactic acids are not water soluble beyond 276 (3 repeat units)." These polymers clearly fall within the scope of the claimed subject-matter (see for instance page 22, 2nd full paragraph).

For the sake of completeness, applicants' attention is drawn to the fact that D1discloses all the elements of the preferred embodiments of the application: water as a dispersing adjuvant (see page 11, lines 26 to 29) and treated a dry pre-dispersed composite with an SPC fluid (see page 12, lines 7 to 8). Furthermore, the problem underlying the application of providing composites having prolonged release appears to be common in the art.

CLAIMS

1. A process for the preparation of a polymer composite comprising internally distributed deposition matter wherein the process comprises
providing a deposit of deposition matter at the surface of a solid state polymer substrate by spraying or immersing solid state polymer substrate by immersing with a solution, dispersion or suspension of deposition matter for a time of the order of 1 second up to 48 hours,
drying for a time up to 48 hours by freezing, evaporation, heating or blotting whereby the deposition matter adsorbs from liquid phase on to the polymer surface and forms an adsorption layer of deposition matter which is intact to solvent and impact effects
contacting the surface deposited polymer with a plasticising fluid or a mixture of plasticising fluids under plasticising conditions to plasticise and/or swell the polymer and internally distribute deposition matter, and
releasing the plasticising fluid or fluids to obtain polymer composite.

2. A process as claimed in Claim 1 which comprises providing a deposit at the surface of a high surface area polymer substrate.

3. Process as claimed in Claim 2 wherein the polymer substrate comprises a powder bed or a high porosity matrix.

4. A process as claimed in any of Claims 1 to 3 wherein a deposit comprises a deposition layer of deposition matter on any internal and external exposed surfaces of the polymer substrate, including any exposed surface pores; over the entire surface area or only part or parts thereof.

5. A process as claimed in any of Claims 1 to 4 wherein the solid state polymer substrate is obtained by contacting polymer with plasticising fluid or a mixture of plasticising fluids under plasticising conditions to plasticise the polymer, and releasing the fluid in manner to obtain a solid state substrate polymer.

6. A process as claimed in any of Claims 1 to 4 wherein deposition matter comprises avidin tagged with rhodamine or ribonuclease and a solution of deposition matter is at concentration of 1 – 250 microgram per ml in distilled water or any liquid that dissolves the biological molecule but does not dissolve the polymer, and is pipetted onto polymer and remains in contact with polymer for a period of between 1 second and 48 hours, during which freeze-drying is used to remove the liquid.

7. A process as claimed in any of Claims 1 to 6 carried out in the absence of additional solvent capable of dissolving the deposition matter.

8. A process as claimed in any of Claims 1 to 7 wherein plasticising conditions comprise a temperature in the range –200°C to +500°C, preferably –200°C to 200°C.

9. A process as claimed in any of Claims 1 to 8 wherein plasticising conditions comprise a pressure from in excess of 1 bar to 10000 bar, preferably 1 to 1000 bar.

10. A process as claimed in any of Claims 1 to 9 wherein the process is carried out for a contact time of surface deposited polymer and plasticising fluid of 1 millisecond up to 5 hours.

11. A process as claimed in any of Claims 1 to 10 which is carried out without blending.

12. A process as claimed in any of Claims 1 to 11 wherein releasing the plasticising fluid(s) comprises prolonged gradual release of plasticising fluid giving transition to near ambient pressure conducted over a depressurisation period of in excess of 10 minutes up to 12 hours giving prolonged gradual transition for non-porous polymer, or over a period of from 1 ms to 10 minutes giving rapid transition for high porosity polymer.

13. A process as claimed in any of Claims 1 to 12 wherein plasticising fluid is selected from carbon dioxide, di-nitrogen oxide, carbon disulphide, aliphatic C_{2-10} hydrocarbons such as ethane, propane, butane, pentane, hexane, ethylene, and halogenated derivatives thereof such as for example carbon tetrafluoride or chloride and carbon monochloride trifluoride, and fluoroform or chloroform, C_{6-10} aromatics such as benzene, toluene and xylene, C_{1-3} alcohols such as methanol and ethanol, sulphur halides such as sulphur hexafluoride, ammonia, xenon, krypton, and mixtures thereof.

14. A process as claimed in any of Claims 1 to 13 wherein deposition matter is present in an amount with respect to polymer of $1x10^{-12}$ wt% to 99.9 wt%.

15. A process as claimed in Claim 14 wherein deposition matter is present, presented as concentration of deposition matter on polymer, in low volumes in the range $1x10^{1}$ to $1x10^{3}$ ng/mg.

16. Process as claimed in any of Claims 1 to 15, wherein the polymer composite comprises a porous or non porous polymer throughout which

particulate deposition matter is distributed with uniformity in excess of 98%, and comprising levels of deposition matter, presented as concentration of deposition matter on polymer, in the range $1x10^1$ to $1x10^3$ ng/mg.

17. Process as claimed in any of Claims 1 to 16 wherein the polymer composite comprises a porous or non porous polymer throughout which particulate deposition matter is distributed with uniformity in excess of 98%, and comprising deposition matter particle size of the order of 10 microns, 1 micron or 0.1 microns.

18. A process as claimed in any of Claims 1 to 17 wherein deposition material is selected from (pharmaceutical) drugs and veterinary products; agrochemicals as pest and plant growth control agents; human and animal health products; human and animal growth promoting, structural, or cosmetic products including products intended for growth or repair or modelling of the skeleton, organs, dental structure; absorbent biodeposition materials for poisons, toxins.

19. A process as claimed in any of Claims 1 to 18 wherein deposition matter alternatively or additionally comprises function enhancing components, including naturally occurring or synthetic or otherwise modified growth promoters, biocompatibilisers, vitamins, proteins, glycoproteins, enzymes, nucleic acid, carbohydrates, minerals, nutrients, steroids, ceramics and the like and functioning matter such as spores, viruses, mammalian, plant and bacterial cells.

20. Process as claimed in any of Claims 1 to 19 wherein polymer is selected from: polyesters including poly(lactic acid), poly(glycolic acid), copolymers of lactic and glycolic acid, copolymers of lactic and glycolic acid with poly(ethylene glycol), poly(e-caprolactone), poly(3-hydroxybutyrate),

poly(p-dioxanone), poly(propylene fumarate); poly (ortho esters); polyanhydrides; Poly(amino acids); polyacetals; polyketals; polyorthoesters; Polyphosphazenes; azo polymers; synthetic Non-biodegradable Polymers selected from: Vinyl polymers including polyethylene, poly(ethylene-co-vinyl acetate), polypropylene, poly(vinyl chloride), poly(vinyl acetate), poly(vinyl alcohol) and copolymers of vinyl alcohol and vinyl acetate, poly(acrylic acid) poly(methacrylic acid), polyacrylamides, polymethacrylamides, polyacrylates, Poly(ethylene glycol), Poly(dimethyl siloxane), Polyurethanes, Polycarbonates, Polystyrene and derivatives; and Natural Polymers selected from carbohydrates, polypeptides and proteins.

21. A polymer composite when obtained by the process of any of Claims 1 to 20.

22. A scaffold comprising a polymer composite having internally distributed deposition matter obtained by the process of any of Claims 1 to 20 suitably sized and shaped for a desired application.

23. The use of a polymer composite or a scaffold thereof prepared by the process of any of Claims 1 to 20, for drug delivery, in bioremediation, as a biocatalyst or biobarrier for human or animal or plant matter, as a structural component comprising the polymer and optional additional synthetic or natural metal, plastic, carbon or glass fibre mesh, scrim, rod or like reinforcing for medical or surgical insertion, for insertion as a solid monolith into bone or tissue, as fillers or cements for wet insertion into bone or teeth or as solid aggregates or monoliths for orthopaedic implants such as pins, or dental implants such as crowns.

24. A process for preparing a polymer composite, a polymer composite, a scaffold, or the use thereof substantially as described in the description or illustrated in the Examples.